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NEPHROLOGY - ORIGINAL PAPER

Desmopressin for the prevention of bleeding in percutaneous kidney biopsy: efficacy and hyponatremia

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Abstract

Background Desmopressin is used to reduce bleeding complications for kidney biopsies with azotemia but little is known about desmopressin-induced hyponatremia in these individuals. We aimed to evaluate the impact of desmopressin prophylaxis on severe hyponatremia and bleeding after kidney biopsies in individuals with renal impairment.

Method This is a single-center retrospective cohort study of consecutive adults with serum creatinine ≥ 150 µmol/L and had ultrasound-guided percutaneous native or transplant kidney biopsies between June 2011 and July 2015. Data were retrieved from electronic medical records. Primary outcomes were the use of desmopressin prophylaxis and severe hyponatremia (serum sodium ≤ 125 mmol/L) within 7 days post-biopsy. Secondary outcome was post-biopsy bleeding.

Results 240 native kidney and 196 allograft biopsies were performed. Median age was 51 (IQR 42.3, 60) years and eGFR was 21.9 (12.9, 30.1) ml/min/1.73 m^2. Although patients prescribed desmopressin prophylaxis ($n = 226$) had higher serum creatinine [279 (201, 392) vs. 187 (160, 241), $p < 0.001$], bleeding (15.0% vs. 13.3%, $p = 0.60$) was not significantly different with and without desmopressin. Severe hyponatremia occurred in 30 biopsies (6.9%) with nadir serum sodium level of 122 (119, 124) mmol/L at 3 (2, 5) days after biopsy, more frequently among those with desmopressin prophylaxis (10.7% vs. 3.0%, $p = 0.002$). Multi-variate analysis found that pre-biopsy serum sodium level [adjusted OR 0.80 (95% CI 0.72, 0.90), $p < 0.001$] and desmopressin prophylaxis [adjusted OR 4.02 (95% CI 1.58, 10.21), $p = 0.003$] were independently associated with severe hyponatremia after kidney biopsy.

Conclusion Pre-biopsy desmopressin was associated with severe hyponatremia in individuals with renal impairment; hence, susceptible patients given desmopressin should be closely monitored.

Keywords Glomerulonephritis · Needle biopsy · Electrolyte · Chronic kidney disease

Introduction

Glomerulonephritis is one of the leading causes of end-stage renal failure worldwide and a kidney biopsy is the gold standard for its accurate diagnosis, so that appropriate therapy can be instituted [1, 2]. However, this procedure is associated with bleeding complications, especially in patients with renal impairment due to uremia-mediated platelet dysfunction [3]. Desmopressin reduces bleeding time and uremic bleeding, and has been recommended pre-biopsy for individuals with azotemia [4–6]. However, desmopressin can predispose to hyponatremia as it is a synthetic vasopressin receptor agonist that increases water reabsorption from urine in the collecting ducts [7]. Desmopressin-induced severe hyponatremia in patients with hemophilia, von Willebrand factor deficiency and other bleeding disorders undergoing invasive procedures have caused acute confusion, seizures and prolonged hospitalization [8–12]. There are scant data and lack of consensus on the clinical use and safety of desmopressin for prophylaxis against post-biopsy bleeding in native kidney and allograft biopsies in individuals with chronic kidney disease (CKD) [13, 14]. In particular, individuals with uremia most likely to receive desmopressin for prophylaxis against bleeding complications may also be

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at greater risk of developing severe hyponatremia due to prolonged desmopressin half-life in renal dysfunction and concurrent diuretic therapy commonly prescribed in CKD [15]. We aimed to evaluate the utilization of desmopressin prophylaxis and its impact on the occurrence of severe hyponatremia and bleeding after ultrasound-guided percutaneous kidney biopsies in individuals with renal impairment.

Methods

Study population

This was a single-center retrospective study of consecutive adults ≥ 21 years with serum creatinine ≥ 150 µmol/L and had a percutaneous ultrasound-guided biopsy of either a native or a transplant kidney in our center between 2nd June 2011 and 31st July 2015. Patients were identified from a procedure log that recorded all percutaneous kidney biopsies performed by nephrologists and interventional radiologists in our institution. All biopsies were performed based on clinical indications. Relative contraindications to biopsy include SBP > 160 mmHg and use of antiplatelet or anticoagulation therapy. Renal function and electrolytes, full blood count and coagulation profile with activated partial thromboplastin time (aPTT) and prothrombin time (PT) were routinely performed prior to kidney biopsy. Desmopressin use was physician dependent but was suggested for patients with serum urea > 15 mmol/L or serum creatinine > 200 µmol/L or estimated glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2. Desmopressin prophylaxis was administered as a single intravenous dose within an hour before kidney biopsy. All patients were admitted and routinely observed for at least 24 h post-biopsy. All biopsies were performed under direct ultrasound guidance using a 16-gauge automated spring-loaded gun (Bard® Magnum® Reusable Core Biopsy System, Bard Biopsy Systems, United States; or BioPince™ Full Core Biopsy Instrument, Argon Medical Devices, United States). Adequacy of samples was confirmed immediately by a trained laboratory technician using light microscopy. Following the biopsy, patients had to lie supine for at least 6 h and observed for at least 24 h for gross hematuria, flank pain, tachycardia and hypotension. Electrolyte, blood count and kidney imaging were requested based on clinical indications.

Risk factor and outcome definitions

Demographic, co-morbidity (physician-diagnosed diabetes mellitus and hypertension, pre-biopsy systolic and diastolic blood pressure, weight), type of kidney biopsy (native or transplant allograft kidney), laboratory (pre-biopsy hemoglobin, PT, aPTT, platelet, serum sodium urea, creatinine, urine protein–creatinine ratio and post-biopsy hemoglobin and serum sodium) and pre-biopsy medication (desmopressin prescription and dose, thiazide or loop diuretic, antihypertensive, antiplatelet or anticoagulant) that may be associated with either hyponatremia or bleeding were retrieved from electronic medical records [3]. As full blood count, coagulation profile and electrolytes are mandated a day before or on the day of biopsy as part of routine clinical practice, pre-biopsy hemoglobin, PT, aPTT, platelet, serum sodium, urea and creatinine were defined as the values within 48 h before biopsy. Other pre-biopsy laboratory values were defined as the most recent value within 30 days prior to kidney biopsy. All laboratory investigations were performed in the central laboratory which is accredited by the College of American Pathologists. Estimated GFR was calculated using the CKD EPI equation [16].

Primary outcomes were (1) use of desmopressin prophylaxis and (2) severe hyponatremia (serum sodium ≤ 125 mmol/L) within 7 days post-biopsy. The secondary outcome was post-biopsy bleeding, which included both minor and major bleeding events. Minor bleed was defined as gross hematuria, radiology-confirmed perinephric hematoma and reduction in hemoglobin (Hb) > 20%; major bleeding was defined as need for red cell transfusion, radiological or surgical intervention; or if bleeding was either a direct, intervening, contributory or originating antecedent cause of death [17], Although there are scanty data on the epidemiology of desmopressin-related hyponatremia in kidney biopsy, there are case reports or small series of patients with bleeding disorders (and presumably normal kidney function) prescribed single-dose prophylactic desmopressin for other indications such as surgery, where symptomatic severe hyponatremia typically developed within 2 days after exposure [9, 18–20]. Our patients with CKD may possibly present later with symptomatic hyponatremia, since the half-life of desmopressin is prolonged up to three times in renal impairment and electrolytes were not routinely performed post-biopsy [15]. However, late-onset hyponatremia (> 7 days after kidney biopsy) was considered less likely to be causally related to pre-biopsy use of desmopressin. Patient outcomes were recorded until their last visit or death before 30th October 2017.

This study abided by the Declaration of Helsinki and waiver of informed consent for this retrospective electronic medical records review was approved by the local Institutional Review Board (CIRBE 2017/2647).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 21.0 (IBM Corp., Armonk, New York). Categorical variables were presented as proportions and continuous variables summarized as medians with interquartile ranges [IQR

(25th percentile, 75th percentile)]. Pearson Chi-square test or Fisher's exact test was used to compare categorical variables and Mann–Whitney *U* test for non-normally distributed continuous variables. Binary logistic regression analysis (stepwise method) was used to calculate odds ratio (OR) and 95% confidence interval (CI) for factors associated with outcomes. Co-variates were chosen if *p* value were < 0.10 on uni-variate analysis. All analyses were two-tailed and *p* values < 0.05 were considered as statistically significant.

Results

Study population

Two hundred and forty native kidney biopsies were performed for 240 patients and 196 allograft biopsies were performed for 143 kidney transplant recipients with baseline serum creatinine ≥ 150 µmol/L. Median age at the time of biopsy was 51.3 (IQR 42.3, 60.0) years and the multi-ethnic cohort reflected the ethnic distribution of the residential population: 318 Chinese (72.9%), 79 Malay (18.1%), 25 Indian (5.7%) and 14 other ethnicities (3.2%). The majority had moderately impaired renal function with eGFR < 30 ml/min/1.73 m^2 in 324 (74.3%) biopsies. Co-morbid disease, pre-biopsy clinical parameters and medications are shown in Table 1. Diuretic therapy was common among these individuals with renal impairment. Pre-biopsy, 66 (15.1%) had mild hyponatremia with serum sodium between 130 and 135 mmol/L but none had severe hyponatremia. Mild hyponatremia before biopsy was associated with elderly (age ≥ 65 years in 27.3% versus 13.2%, $p = 0.004$) but not with moderate-severe renal impairment (serum creatinine ≥ 250 µmol/L in 45.5% versus 39.5%, $p = 0.36$) or

Table 1 Characteristics and outcomes of percutaneous native and allograft kidney biopsies compared according to the use of prophylactic desmopressin pre-biopsy

	All biopsy episodes, *N* = 436	No desmopressin, *N* = 210	Desmopressin, *N* = 226	*p* value[a]
Age, years	51.3 (42.3, 60.0)	51.3 (42.5, 59.2)	51.5 (41.8, 61.1)	0.46
Male, *n* (%)	248 (56.9)	128 (61.0)	120 (53.1)	0.10
Co-morbid disease				
Diabetes mellitus, *n* (%)	139 (31.9)	63 (30.0)	76 (33.6)	0.42
Hypertension, *n* (%)	344 (78.9)	164 (78.1)	180 (79.6)	0.69
Systolic BP, mmHg	130 (120, 143)	130 (120, 140)	130 (120, 146)	0.38
Diastolic BP, mmHg	75 (70, 80)	77 (70, 80)	74 (70, 80)	0.92
Weight, kg	67.4 (57.5, 79.0)	67.8 (57.9, 79.0)	67.0 (57.3, 79.2)	0.72
Medications				
Anti-hypertensive therapy, *n* (%)	358 (82.1)	177 (84.3)	181 (80.1)	0.25
Diuretic, *n* (%)	174 (39.9)	66 (31.4)	108 (47.8)	< 0.001
Thiazide, *n* (%)	23 (5.3)	12 (5.7)	11 (4.9)	0.70
Loop diuretic, *n* (%)	154 (35.3)	55 (26.2)	99 (43.8)	< 0.001
Pre-biopsy laboratory				
Hemoglobin, g/dL	10.7 (9.5, 12.2)	11.3 (10.0, 12.8)	10.2 (9.2, 11.4)	< 0.001
Serum sodium, mmol/L	138 (136, 139)	138 (136, 140)	137 (132, 139)	0.46
Serum urea, mmol/L	13.0 (9.6, 16.9)	10.3 (8.1, 13.5)	15.2 (12.3)	< 0.001
Serum creatinine, µmol/L	225 (170, 324)	187 (160, 241)	279 (201, 392)	< 0.001
eGFR, ml/min/1.73 m^2	21.9 (12.9, 30.1)	27.3 (18.0, 36.5)	16.9 (9.9, 23.2)	< 0.001
Urine PCR, g/g	3.1 (0.9, 6.4)	2.7 (0.7, 5.8)	3.2 (1.0, 6.7)	0.11
Outcomes				
Bleeding, *n* (%)	62 (14.2)	28 (13.3)	34 (15.0)	0.60
Severe hyponatremia, *n* (%)	30 (6.9)	6 (3.0)	24 (10.7)	0.002
Bleed with severe hyponatremia, *n* (%)	5 (1.1)	1 (0.5)	4 (1.8)	0.20
Bleed and no severe hyponatremia, *n* (%)	57 (13.1)	27 (12.9)	30 (13.3)	0.89
No bleed with severe hyponatremia, *n* (%)	25 (5.7)	5 (2.4)	20 (8.8)	0.004

Categorical variables are presented as proportions and continuous variables as medians with interquartile ranges [IQR (25th percentile, 75th percentile)]. Pearson Chi-square test or Fisher's exact test was used to compare categorical variables and Mann–Whitney *U* test for non-normally distributed continuous variables

BP blood pressure, *eGFR* estimated glomerular filtration rate, *PCR* protein–creatinine ratio

[a]*p* values are for comparison between desmopressin and no desmopressin groups

diuretic use (39.4% versus 40.0%, $p = 0.92$). Median follow-up duration was 39.0 (27.3, 53.4) months after kidney biopsy.

Desmopressin prophylaxis before kidney biopsy

Desmopressin prophylaxis was administered for 128 native kidney biopsies and 98 allograft biopsies. Figure 1 shows the proportion of biopsies who received prophylactic desmopressin, categorized according to baseline renal function: (a) serum urea > 15 mmol/L (b) serum creatinine ≥ 200 µmol/L (c) CKD EPI eGFR < 30 ml/min/1.73 m^2. The large proportion of patients administered prophylactic desmopressin likely reflects recommendations described in Methods. Median desmopressin dose was 0.20 (0.17, 0.24) µg/kg body weight. Patients prescribed desmopressin prophylaxis had worse renal function, lower pre-biopsy hemoglobin levels and more had concurrent diuretic use (Table 1). Baseline serum sodium was not significantly different between the two groups.

Hyponatremia after kidney biopsy

Post-procedure electrolytes were performed in 423 biopsies and hyponatremia was noted in 168 biopsies within 7 days (39.4%). Severe hyponatremia occurred in 30 biopsies (6.9%) with nadir serum sodium level of 122 (119, 124) mmol/L at 3 (2, 5) days after biopsy. In determining severe hyponatremia outcome status for those without post-biopsy electrolytes within 7 days after biopsy, we considered that despite the lack of serum sodium value for the first week post-biopsy, all those with missing values remained on active follow-up with our institution in the subsequent weeks after biopsy and were, thus, unlikely to have developed symptomatic severe hyponatremia, in which case they would have presented to our institution for evaluation. Moreover, missing value imputation using the mean post-biopsy nadir sodium level of 133 mmol/L also resulted in those with missing values to be assigned as "without severe hyponatremia".

Severe hyponatremia was more common among those with desmopressin prophylaxis than those without, as was the combined outcome of post-biopsy severe hyponatremia without bleeding complication (Table 1).

Comparing individuals who developed severe hyponatremia post-biopsy with those who did not, those who had severe hyponatremia had greater renal impairment [eGFR 15.3 (10.6, 23.6) versus 22.3 (13.2, 30.7) ml/min/1.73 m^2, $p = 0.03$], lower pre-biopsy serum sodium levels [135 (132, 137] versus 138 (136, 140) mmol/L, $p < 0.001$] and more received desmopressin prophylaxis (80.0% versus 49.8%, $p = 0.001$) at higher doses [0.25 (0.20, 0.28) versus 0.19 (0.17, 0.24) µg/kg body weight, $p = 0.002$] than those who did not have severe hyponatremia post-biopsy. Use of diuretic therapy was not different between the groups (36.7% versus 40.1%, $p = 0.70$).

Unadjusted and adjusted OR and 95% CI for factors associated with severe hyponatremia are shown in Table 2. Multi-variate logistic regression found that pre-biopsy serum sodium level and desmopressin prophylaxis were independently associated with severe hyponatremia after kidney biopsy. Sensitivity analysis performed by excluding those

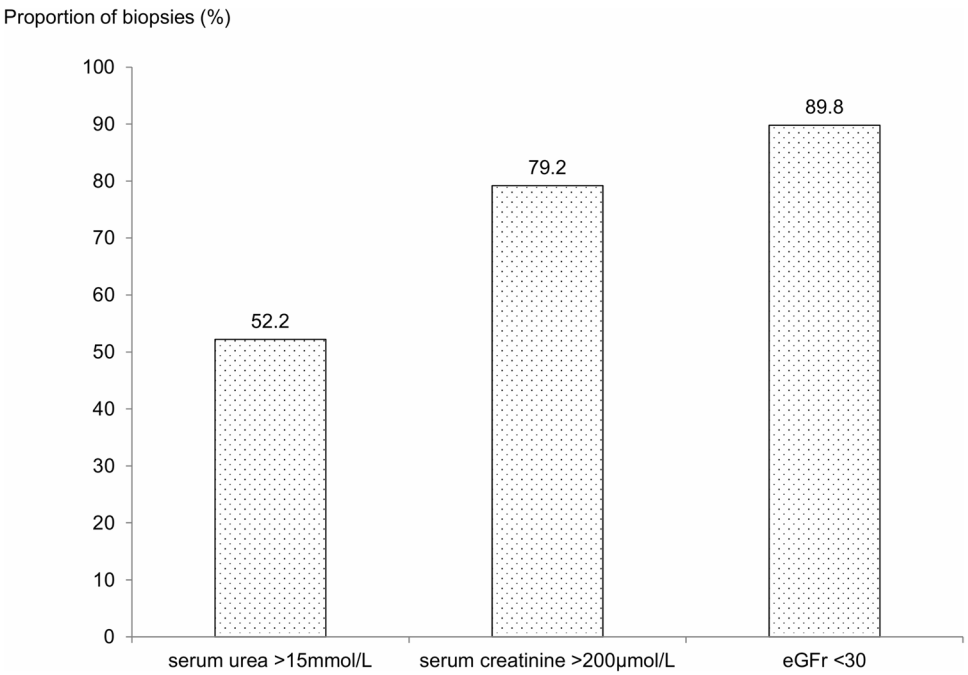

Fig. 1 Proportion of biopsies pre-treated with prophylactic desmopressin, categorized according to pre-biopsy renal function. *eGFR* estimated glomerular filtration rate in mL/min/1.73 m^2

Table 2 Factors associated with severe hyponatremia (serum sodium ≤ 125 mmol/L) within 7 days post-kidney biopsy

	Univariate OR (95% CI)	*p* value	Multivariate OR (95% CI)	*p* value
Age ≥ 65 years	0.84 (0.28, 2.48)	0.74	–	
Male gender	0.85 (0.40, 1.80)	0.68	–	
Hypertension	0.50 (0.23, 1.12)	0.10	–	
Diabetes	0.76 (0.33, 1.76)	0.52	–	
Weight per 1 kg increase	0.99 (0.96, 1.01)	0.44	–	
Diuretic therapy	0.86 (0.40, 1.86)	0.70	–	
Desmopressin	4.04 (1.61, 10.09)	0.003	4.02 (1.58, 10.21)	0.003
Pre-biopsy serum sodium, per 1 mmol/L increase	0.80 (0.72, 0.89)	< 0.001	0.80 (0.72, 0.90)	< 0.001
eGFR, per 1 ml/min/1.73 m^2	0.96 (0.93, 0.99)	0.03	0.97 (0.94, 1.01)	0.21
Allograft kidney, compared to native kidney	1.43 (0.68, 3.01)	0.34	–	

Binary logistic regression analysis (stepwise method) was used to calculate odds ratio (OR) and 95% confidence interval (CI) for factors associated with outcomes

eGFR estimated glomerular filtration rate

Co-variates were chosen if *p* value was < 0.10 on uni-variate analysis

without post-biopsy serum sodium values confirmed that pre-biopsy serum sodium levels [adjusted OR 0.80, 95% CI (0.72, 0.89), $p < 0.001$] and desmopressin use [adjusted OR 3.84, 95% CI (1.51, 9.76), $p = 0.005$] remain independently associated with severe hyponatremia after kidney biopsy. In subgroup analysis, desmopressin use remained associated with severe hyponatremia for individuals with milder renal impairment with baseline serum creatinine between 150 and 250 µmol/L [adjusted OR 4.72, 95% CI (1.19, 18.66), $p = 0.02$] but not in those with more severe renal impairment with serum creatinine ≥ 250 µmol/L [adjusted OR 1.78, 95% CI (0.48, 6.63), $p = 0.38$].

Bleeding events after kidney biopsy

Cumulative incidence of all bleeding events, namely gross hematuria, radiology-confirmed perinephric hematoma, reduction in hemoglobin > 20%, need for red cell transfusion and bleeding that required radiological or surgical intervention was 14.2% (62 biopsies), while major bleed occurred in 26 biopsies (5.9%) and minor bleed occurred in 58 (13.3%). Post-biopsy perinephric hematoma and gross hematuria occurred in 39 (9.0%) and 17 (3.9%) biopsies, respectively, while red cell transfusion and radiological intervention were required in 25 (5.7%) and 3 (0.7%) biopsies, respectively; there was no bleeding-related nephrectomy or death.

There were no significant differences in the occurrence of minor bleeding (13.7% versus 12.9%, $p = 0.79$) and major bleeding (7.5% versus 4.3%, $p = 0.15$) in those with prophylactic desmopressin compared to those without. Figure 2 shows all bleeding events and major bleed with and without prophylactic desmopressin, categorized according to baseline kidney function. Patients with poorer renal function given prophylactic desmopressin tended to have fewer bleeding events but the differences were not statistically significant.

Comparing biopsies with and without post-biopsy bleeding (Table 3), bleeding and major bleeding were more likely to occur in native kidney biopsies, diabetics, lower pre-biopsy hemoglobin and platelet levels and higher aPTT levels; in addition, major bleeding was more likely to occur in those with higher urea and creatinine levels. Multi-variate logistic regression found that allograft kidney biopsies [OR 0.35, 95% CI (0.19, 0.65), $p = 0.001$) and individuals with higher pre-biopsy hemoglobin [OR 0.84 (95% CI 0.72, 0.97) per 1 g/dL increment, $p = 0.002$] and platelet levels [OR 0.995 (95% CI 0.991, 0.995), $p = 0.003$] were less likely to have post-biopsy bleeding. There was only 1 patient with renal amyloidosis in this cohort; this individual received prophylactic desmopressin and did not have post-biopsy bleeding. A multi-variate analysis was not performed for major bleeding since there were only 26 events.

Discussion

We evaluated 436 native and allograft kidney biopsies and found that prophylactic desmopressin was frequently used for patients with renal impairment undergoing percutaneous kidney biopsy but was independently associated with severe hyponatremia after biopsy.

In addition, native kidney biopsies and lower pre-biopsy hemoglobin and platelet levels were independently associated with bleeding among these individuals. In a systematic review and meta-analysis of bleeding complications in 9474 adult native kidney biopsies, lower baseline hemoglobin was associated with erythrocyte transfusion but not macroscopic hematuria [3]. Although both bleeding and

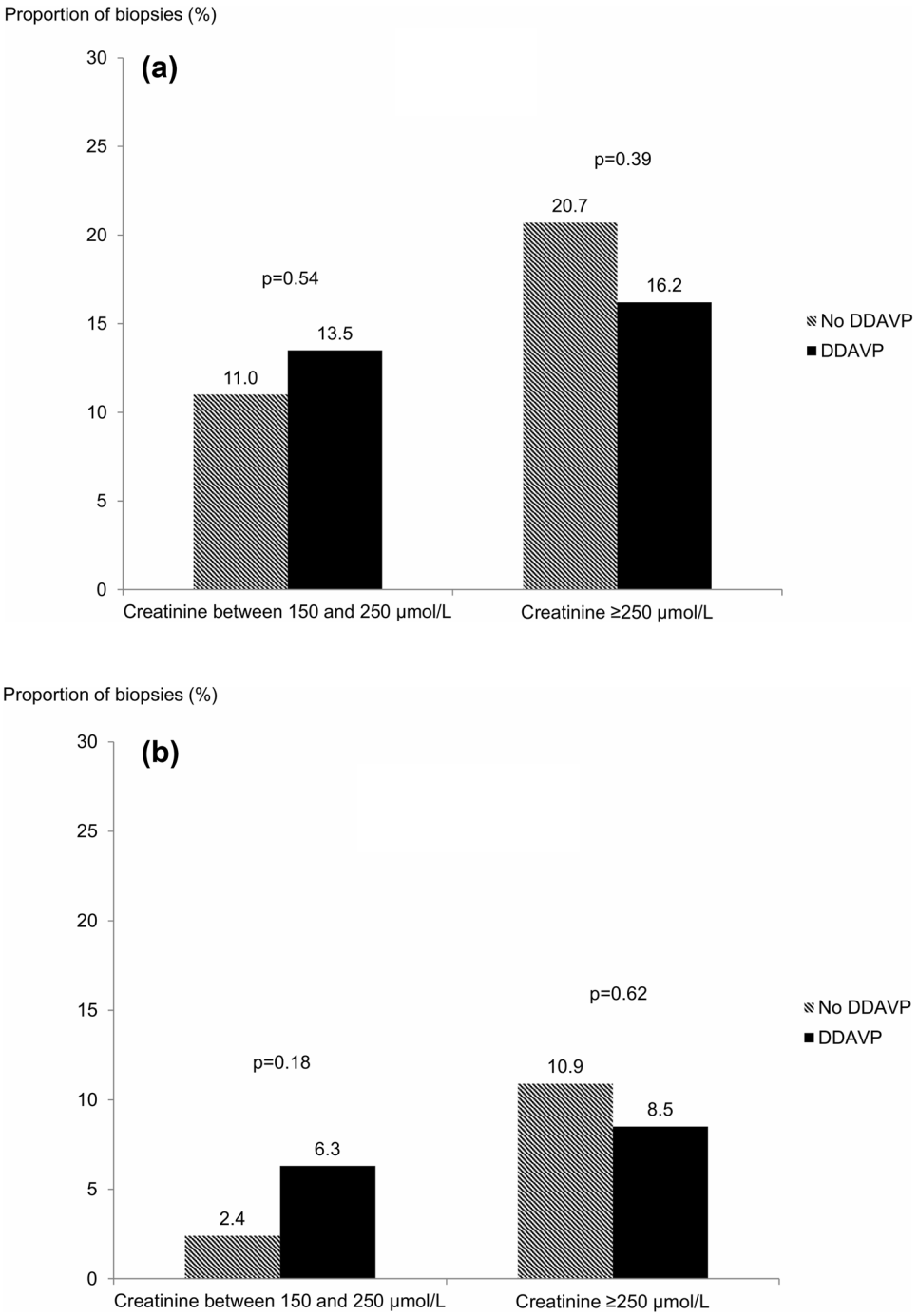

Fig. 2 Proportion of biopsies with **a** bleeding events and **b** major bleed after kidney biopsy, categorized according to pre-biopsy kidney function. Chi-square test was used to compare bleeding risk without and with desmopressin prophylaxis; p values < 0.05 were considered statistically significant

major bleeding were more frequent among native kidney biopsies in our study, prior studies that compared risk of bleeding in native and transplant allograft biopsies had conflicting results that may be due to differences in center practices and biopsy volumes [21, 22]. A recent systematic review and analysis with meta-regression comparing pediatric native biopsies with transplant biopsies did not identify biopsy type to be associated with the need for a blood transfusion or requirement of an additional intervention after biopsy [23].

Higher serum urea and creatinine levels pre-biopsy were associated with major bleeding in our study, consistent with existing literature such as the aforementioned systematic review of adult native kidney biopsies where erythrocyte transfusion rates were higher in studies with mean serum creatinine ≥ 2.0 mg/dL (2.1% versus 0.4%, $p = 0.02$) [3]. Thus, bleeding risk should be greater in the group which received desmopressin and had a greater degree of renal impairment, yet bleeding was comparable in the two groups (Table 1). In addition, bleeding tended to be less frequent

Table 3 Comparison of biopsies with and without bleeding and major bleed after kidney biopsy

	Post-biopsy Bleed			Major bleed		
	No, $N=374$	Yes, $N=62$	p value[a]	No, $N=410$	Yes, $N=26$	p value[b]
Age, years	50.8 (41.9, 59.5)	53.2 (43.5, 62.9)	0.14	50.9 (41.9, 59.4)	59.3 (45.7, 66.7)	0.01
Male, *n* (%)	215 (57.5)	33 (53.2)	0.53	235 (57.3)	13 (50.0)	0.46
Co-morbid disease						
Diabetes mellitus, *n* (%)	112 (29.9)	27 (43.5)	0.03	125 (30.5)	14 (53.8)	0.01
Hypertension, *n* (%)	292 (78.1)	52 (83.9)	0.30	322 (78.5)	22 (84.6)	0.46
Systolic BP, mmHg	130 (120, 143)	136 (120, 145)	0.58	130 (120, 143)	135 (112, 145)	0.80
Diastolic BP, mmHg	77 (70, 80)	70 (68, 80)	0.39	75 (70, 80)	71 (67, 80)	0.73
Medications						
Anti-platelet, *n* (%)	4 (1.1)	0	0.41	4 (1.0)	1 (3.8)	0.61
Anti-coagulant, *n* (%)	2 (0.5)	2 (3.2)	0.04	3 (0.7)	1 (3.8)	0.10
Anti-hypertensive therapy, *n* (%)	312 (83.4)	46 (74.2)	0.08	337 (82.2)	21 (80.8)	0.85
Desmopressin, *n* (%)	192 (51.3)	34 (54.8)	0.61	209 (61.0)	17 (65.4)	0.15
Desmopressin dose, µg per kg body weight	0.20 (0.17, 0.24)	0.21 (0.18, 0.25)	0.32	0.20 (0.17, 0.24)	0.23 (0.19, 0.26)	0.12
Pre-biopsy laboratory						
Hemoglobin, g/dL	10.8 (9.6, 12.2)	9.8 (8.8, 11.5)	0.01	10.8 (9.6, 12.2)	9.3 (8.4, 10.1)	< 0.001
Prothrombin time,	10.3 (9.9, 10.7)	10.3 (9.8, 10.9)	0.63	10.3 (9.9, 10.6)	10.9 (10.2, 11.4)	0.001
aPTT, sec	27.2 (25.8, 28.9)	28.1 (25.9, 30.8)	0.03	27.2 (25.8, 29.1)	28.5 (26.3, 33.0)	0.03
Platelet, number $\times 10^9$/L	252 (200, 312)	219 (172, 272)	0.003	251 (200, 308)	192 (132, 245)	< 0.001
Serum urea, mmol/L	12.9 (9.6, 16.7)	13.3 (10.5, 17.4)	0.20	12.9 (9.6, 16.7)	17.0 (12.8, 19.7)	0.009
Serum creatinine, µmol/L	222 (169, 320)	243 (181, 331)	0.25	222 (169, 320)	296 (200, 416)	0.04
eGFR, ml/min/1.73 m^2	22.3 (13.4, 30.4)	18.1 (10.6, 28.2)	0.10	22.2 (13.4, 30.7)	13.7 (5.5, 23.1)	0.003
Type of kidney, n (%)						
Native	196 (52.4)	44 (71.0)	0.007	220 (53.7)	20 (76.9)	0.02
Transplant	178 (47.6)	18 (29.0)		190 (46.3)	6 (23.1)	

Categorical variables are presented as proportions and continuous variables as medians with interquartile ranges [IQR (25th percentile, 75th percentile)]. Pearson Chi-square test or Fisher's exact test was used to compare categorical variables and Mann–Whitney *U* test for non-normally distributed continuous variables

BP blood pressure, *eGFR* estimated glomerular filtration rate, *aPTT* activated partial thromboplastin time

[a]*p* values are for comparison between post-biopsy bleed and no bleed groups

[b]*p* values are for comparison between post-biopsy major bleed and no major bleed groups

in the subgroup with serum creatinine ≥ 250 µmol/L given prophylactic desmopressin. Hence, desmopressin appears to attenuate bleeding risk in our patients with severe renal impairment. Although there is no consensus on its use and the body of evidence is not large [14], desmopressin had previously been demonstrated to reduce bleeding complications in percutaneous kidney biopsies [24, 25], possibly by increasing levels of von Willebrand factor and factor VIII and reducing bleeding time [5]. A randomized controlled study by Manno et al. found that post-biopsy bleeding was reduced with subcutaneous desmopressin prophylaxis at 0.3 µg/kg body weight when compared to placebo (13.7% versus 30.5%, $p=0.01$) in 162 adults with normal renal function [24]. However, a subsequent observational study did not find desmopressin to affect bleeding complications in patients with eGFR < 30 ml/min [26]. More recently, Peters et al. evaluated registry data for 576 native kidney biopsies with serum creatinine > 150 µmol/L, comparing outcomes from a center that routinely administered desmopressin prophylaxis with centers that did not [25]. On multi-variate analysis adjusting for age, gender and body mass index, desmopressin prophylaxis reduced major bleeding complications [adjusted odds ratio 0.38, 95% CI (0.15, 0.96)]. However, the favorable outcome of desmopressin prophylaxis demonstrated by this study may be confounded by differences in center practices, such as operator experience, biopsy volumes and needle gauge used, other than desmopressin use. Interestingly, both positive studies administered desmopressin subcutaneously while our patients received intravenous desmopressin [24, 25]. It is possible that the route of desmopressin administration may affect its clinical impact. Compared to intravenous administration, the same dose of desmopressin administered subcutaneously to healthy individuals led to a larger area under the curve and

a greater amount of desmopressin excreted in the urine [27]. In addition, hyponatremia was more frequent in intranasal desmopressin than oral administration among patients who received desmopressin treatment for central diabetes insipidus [28].

There is scant literature, other than case reports [29], on the impact of single-dose prophylactic desmopressin on hyponatremia after kidney biopsy. Studies by Manno et al. and Peters et al. that reported reduced bleeding with desmopressin use did not specifically evaluate post-biopsy electrolyte derangements. A historical study of 269 transplant allograft biopsies found that none had symptomatic hyponatremia, although all received pre-biopsy desmopressin and none had symptomatic hyponatremia [30]. However, patients in the study were administered only 4 "units" of desmopressin before biopsy; this dose appears much lower compared to the recommended dose of 0.3 µg/kg body weight administered subcutaneously or intravenously [24, 31]. Despite administering doses below this recommended dose, almost a tenth of our cohort had severe hyponatremia post-biopsy, whereas the incidence of mild hyponatremia after single-dose desmopressin in patients with bleeding disorders ranged from 4 to 10% [9, 12]. Although diuretic use was more frequent among patients administered desmopressin pre-biopsy, multivariate analysis adjusting for diuretic use still found desmopressin to be independently associated with severe hyponatremia. We surmise that our center's historical practice of encouraging fluid hydration in a standard post-procedure checklist, meant to reduce the risk of clot obstruction after kidney biopsy, may have contributed to the high incidence of post-biopsy hyponatremia as it was likely to be applied to all patients without differentiating those who received desmopressin. Other physicians have similarly encouraged oral fluid intake in preparation for allograft kidney biopsies [29]. However, concurrent prescription of desmopressin and hypotonic fluids can cause severe hyponatremia [29]. We have ceased advising patients for aggressive hydration after kidney biopsy, since the patients invariably hydrate with free water.

As severe hyponatremia is associated with significant morbidity and mortality [7], we suggest that desmopressin prophylaxis should be reserved for those with more severe renal impairment and thus at greatest risk of uremic bleeding after biopsy. Interestingly, we found the association between desmopressin and severe hyponatremia to be diminished among those with more severe renal impairment. We postulate that these patients may have reduced nephron mass and greater tubular atrophy with disruption in their medullary osmotic gradient, resulting in attenuated response to the anti-diuretic effect of desmopressin. In addition, desmopressin prophylaxis should be avoided or administered at a reduced dose in individuals with concurrent diuretic medications or had serum sodium levels bordering on or below 135 mmol/L before biopsy. If desmopressin prophylaxis is administered, we suggest restricting free water intake and careful monitoring for symptoms of hyponatremia such as headache, nausea, lethargy and confusion for 72 h after desmopressin administration, based on our finding that sodium nadir levels occurred at a median of 3 days after kidney biopsy in this cohort with renal impairment. In addition, serum sodium should be checked within 24–48 h after desmopressin administration.

Limitations of this study include its retrospective nature; hence, causality cannot be confirmed for these associations. As serum sodium was not routinely measured post-biopsy, asymptomatic mild hyponatremia may be underestimated; however, severe hyponatremia is likely to be symptomatic and easily diagnosed by simple blood tests that are readily available. We were unable to assess potential confounders such as total fluid intake and conditions that affect endogenous vasopressin secretion, such as pain, stress, vomiting and medications such as non-steroidal anti-inflammatory drugs, anti-depressants and neuroleptic agents. We do not routinely perform bleeding time or platelet activation time in our center; hence, these were not included in this study. Although kidney size was not evaluated in this study, significantly reduced kidney size, suggesting kidney atrophy, is a relative contraindication to percutaneous biopsy in our center. Although we do not have data on the number of biopsy passes, we generally do not exceed 4 passes. A meta-analysis of 3804 adult native kidney biopsies from 20 studies found that number of needle passes was not associated with erythrocyte transfusion [3], while a more recent study did not find the number of needle passes to be associated with hemoglobin decline $>10\%$ [22]. We did not examine other potential adverse effects of desmopressin, such as headache, facial flushing, tachycardia, hypotension and thrombosis [12], as they were beyond the scope of this study. As a single-center study, our findings may not be generalizable to other centers with different patient profiles and biopsy practices. However, this study demonstrated the outcomes of desmopressin prophylaxis in real-world nephrology practice outside of clinical trials and highlighted an under-reported adverse event associated with single-dose desmopressin administered to individuals with renal impairment undergoing ultrasound-guided percutaneous kidney biopsies. Future multi-center randomized controlled trials and cost-effectiveness studies may provide stronger evidence for the use of desmopressin prophylaxis for kidney biopsies in patients with mild renal impairment.

Conclusion

Single-dose desmopressin-administered pre-biopsy to individuals with renal impairment was associated with severe hyponatremia after kidney biopsy. We suggest that

desmopressin prophylaxis is reserved for those with severe renal impairment and thus at greater risk of uremic bleed, although the ideal cut-off remains to be determined. Desmopressin should be avoided or dose-attenuated in individuals with low or low–normal serum sodium levels; such patients given desmopressin should be appropriately monitored and counseled on free water restriction.

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Compliance to ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics statement All study procedures, including waiver of informed consent for medical records review, were approved by the institutional research committee and performed in accordance with the 1964 Helsinki declaration.

Informed consent This study abided by the Declaration of Helsinki and waiver of informed consent was approved by the Institutional Review Board (CIRBE 2017/2647).

References

1. Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, Wolfe RA, Jones E, Disney APS, Briggs D et al (2000) Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: results from an international comparative study. Am J Kidney Dis 35(1):157–165
2. Gan L, Zuo L (2015) Current ESRD burden and its future trend in Beijing, China. Clinical nephrology 83(7 Suppl 1):17–20
3. Corapi KM, Chen JL, Balk EM, Gordon CE (2012) Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. Am J Kidney Dis 60(1):62–73
4. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ (2007) Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol 3(3):138–153
5. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmerman TS (1983) Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. N Engl J Med 308(1):8–12
6. Luciano RL, Moeckel GW (2019) Update on the Native Kidney Biopsy: Core Curriculum 2019. Am J Kidney Dis 73(3):404–415
7. Achinger SG, Arieff AI, Kalantar-Zadeh K, Ayus JC (2014) Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series. Nephrol Dial Transplant 29(12):2310–2315
8. Trigg DE, Stergiotou I, Peitsidis P, Kadir RA (2012) A systematic review: the use of desmopressin for treatment and prophylaxis of bleeding disorders in pregnancy. Haemophilia 18(1):25–33
9. Sharma R, Stein D (2014) Hyponatremia after desmopressin (DDAVP) use in pediatric patients with bleeding disorders undergoing surgeries. J Pediatr Hematol Oncol 36(6):e371–375
10. Federici AB (2008) The use of desmopressin in von Willebrand disease: the experience of the first 30 years (1977–2007). Haemophilia 14(Suppl 1):5–14
11. Desborough MJ, Oakland K, Brierley C, Bennett S, Doree C, Trivella M, Hopewell S, Stanworth SJ, Estcourt LJ (2017) Desmopressin use for minimising perioperative blood transfusion. Cochrane Database Syst Rev 7:001884
12. Stoof SC, Cnossen MH, de Maat MP, Leebeek FW, Kruip MJ (2016) Side effects of desmopressin in patients with bleeding disorders. Haemophilia 22(1):39–45
13. Hogan JJ, Mocanu M, Berns JS (2016) The native kidney biopsy: update and evidence for best practice. CJASN 11(2):354–362
14. Bollee G, Martinez F, Moulin B, Meulders Q, Rougier JP, Baumelou A, Glotz D, Subra JF, Ulinski T, Vrigneaud L et al (2010) Renal biopsy practice in France: results of a nationwide study. Nephrol Dial Transplant 25(11):3579–3585
15. Agersø H, Seiding Larsen L, Riis A, Lövgren U, Karlsson MO, Senderovitz T (2004) Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients. Br J Clin Pharmacol 58(4):352–358
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604–612
17. Organization WH (2004) International statistical classification of diseases and related health problems, vol 1. World Health Organization, Berlin
18. Pruthi RS, Kang J, Vick R (2002) Desmopressin Induced Hyponatremia and Seizures After Laparoscopic Radical Nephrectomy. J Urol 168(1):187
19. Davidson HC, Stapleton AL, Casselbrant ML, Kitsko DJ (2011) Perioperative incidence and management of hyponatremia in vWD patients undergoing adenotonsillectomy. Laryngoscope 121(7):1399–1403
20. MacKenzie JS, Kozinn SC (2015) Peri-operative DDAVP use leading to severe hyponatremia after total shoulder replacement in a patient with von Willebrand's disease. HSS Journal 11(3):281–284
21. Gainza FJ, Minguela I, Lopez-Vidaur I, Ruiz LM, Lampreabe I (1995) Evaluation of complications due to percutaneous renal biopsy in allografts and native kidneys with color-coded Doppler sonography. Clin Nephrol 43(5):303–308
22. Šimunov B, Gunjača M, Čingel B, Škegro D, Knotek M (2018) Safety of outpatient kidney biopsies. Nephron 138(4):275–279
23. Varnell CD Jr, Stone HK, Welge JA (2019) Bleeding complications after pediatric kidney biopsy: a systematic review and meta-analysis. CJASN 14(1):57–65
24. Manno C, Bonifati C, Torres DD, Campobasso N, Schena FP (2011) Desmopressin acetate in percutaneous ultrasound-guided kidney biopsy: a randomized controlled trial. Am J Kidney Dis 57(6):850–855
25. Peters B, Hadimeri H, Molne J, Nasic S, Jensen G, Stegmayr B (2018) Desmopressin (Octostim(R)) before a native kidney biopsy can reduce the risk for biopsy complications in patients with impaired renal function: a pilot study. Nephrology (Carlton, Vic) 23(4):366–370
26. Deipolyi A, Leonardo F, Hahn PF, Tan CS, Thabet A, Halpern EF, Mueller PR, Ganguli S (2016) Predictors of hemorrhagic complications after ultrasound-guided nonfocal renal biopsy. J Prev Epidemiol 1:2

27. Fjellestad-Paulsen A, Höglund P, Lundin S, Paulsen O (1993) Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. Clin Endocrinol 38(2):177–182
28. Kataoka Y, Nishida S, Hirakawa A, Oiso Y, Arima H (2015) Comparison of incidence of hyponatremia between intranasal and oral desmopressin in patients with central diabetes insipidus. Endocr J 62(2):195–200
29. Anandagoda N, Jayawardene S, Macdougall IC, Shah S (2014) Desmopressin use prior to renal transplant biopsy-does it fit? Clin Kidney J 7(6):602–604
30. Tsai SF, Chen CH, Shu KH, Cheng CH, Yu TM, Chuang YW, Huang ST, Tsai JL, Wu MJ (2016) Current safety of renal allograft biopsy with indication in adult recipients: an observational study. Medicine 95(6):e2816
31. Desborough MJ, Oakland KA, Landoni G, Crivellari M, Doree C, Estcourt LJ, Stanworth SJ (2017) Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. JTH 15(2):263–272